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What explains the differences between centres in the European screening trial? A simulation study



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ABSTRACT

Background: The European Randomised study of Screening for Prostate Cancer (ERSPC) is a multicentre, randomised screening trial on men aged 55–69 years at baseline without known prostate cancer (PrCa) at randomisation to an intervention arm invited to screening or to a control arm. The ERSPC has shown a significant 21% reduction in PrCa mortality at 13 years of follow-up. The effect of screening appears to vary across centres, for which several explanations are possible. We set to assess if the apparent differences in PrCa mortality reduction between the centres can be explained by differences in screening protocols.

Methods: We examined the centre differences by developing a simulation model and estimated how alternative screening protocols would have affected PrCa mortality.

Results: Our results showed outcomes similar to those observed, when the results by centres were reproduced by simulating the screening regimens with PSA threshold of 3 versus 4 ng/ml, or screening interval of two versus four years. The findings suggest that the differences are only marginally attributable to the different screening protocols.

Conclusion: The small screening impact in Finland was not explained by the differences in the screening protocols. A possible reason for it was the contamination of and the unexpectedly low PrCa mortality in the Finnish control arm.

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1. Introduction

The European Randomised study of Screening for Prostate Cancer (ERSPC) is a multicentre, randomised screening trial assessing mortality from prostate cancer (PrCa) in an intervention arm invited to prostate-specific antigen (PSA)-based screening compared with a control arm without intervention. The trial was initiated in 1993–1996 in seven European countries (N = 162,243): the Netherlands, Sweden and Finland (responsible for 78% of the total number of men included), and smaller centres in Switzerland, Belgium, Italy and Spain. In an updated analysis, the ERSPC has

recently shown a significant 21% reduction in PrCa mortality at 13 years of follow-up [1].

Interestingly, the screening effect does not appear to be constant across the trial centres, with the largest reduction in PrCa mortality in Sweden, followed by the Netherlands and a non-significant 10% decrease in Finland [1–4].

We aim to assess if, and to what extent, the apparent differences in PrCa mortality reduction between the centres can be explained by differences in screening protocols. Both Netherlands and Sweden used a PSA threshold of 3 ng/ml as indication for prostate biopsy, while in Finland it was set at 4 ng/ml (with an ancillary test at PSA 3.0–3.9 ng/ml). The screening interval was four years in Finland and the Netherlands, and two years in Sweden. Although PSA is measured in screening at regular intervals in accordance with centre-specific protocols, the PSA level is known to increase with age and any prostate disease. Thus, a screen-positive man

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could have reached the value used as threshold in screening at an earlier time, but this remains unobservable until the protocol-scheduled measurement. The time to detection of an elevated PSA affects the probability of developing advanced disease and the risk increases with less frequent screening or a higher PSA threshold, which may in turn increase PrCa mortality and reduce the screening effect.

To assess the impact of the screening regimen on screening outcomes, we developed a longitudinal model for PSA and a simulation model for the prediction of PrCa death under different hypothetical conditions. The joint use of these two models allowed estimation of the effects of different screening protocols on PrCa mortality in three largest ERSPC centres.

2. Materials and methods

2.1. Data sets analysed

The present analysis was based on 126,829 men aged 55–69 years at baseline without known PrCa at randomisation from the Netherlands, Sweden and Finland, including 55,199 men assigned to the intervention arm. The follow-up time was truncated at 12 years, during which 5565 (10.1%) men were diagnosed with PrCa in the intervention and 4777 (6.7%) in the control arm. A total of 252 (0.4%) men in the intervention arm and 426 (0.6%) men in the control arm died from PrCa. The median age of the participants at randomisation was 59 years, but the Netherlands centre comprised older men (median age 62 years) than those in Sweden and Finland. Full ERSPC study details are given in Schröder et al. [1].

2.2. Statistical methods

We (i) developed and fitted a longitudinal model on PSA depicting the continuous PSA development over time (velocity or doubling time) in men with and without PrCa and (ii) using the estimated PSA levels, simulated the screening and PrCa outcomes under various hypothetical screening protocols. For example, a simulation following the Swedish protocol at all centres should show the potential effect of a two-year screening interval, i.e. to what extent the differences are attributable to the frequency of screening.

The model for PSA development was built and estimated on PSA data obtained in the ERSPC study, and the same data was used to interpolate/predict individual development of PSA. More specifically, a linear mixed model was fitted for PSA (transformed as $\log[\text{PSA} + 1]$) to depict the continuous PSA development of each man with at least one PSA measurement. The fixed effect part of the model consisted of linear and quadratic age, and of an assumed change in the quadratic part five years before the diagnosis of PrCa. The change was allowed to vary according to the Gleason score (<7 , 7 or >7) of the PrCa. Thus, the individual profiles consisted of piecewise exponential components estimated from the data, allowing a rapid increase starting five years before the diagnosis of PrCa. The choice of five years was based on initial empirical investigation of the data, choosing alternative annual change points and taking the change point which fitted the data best. Man-specific random effects were introduced for the intercept, linear and quadratic terms in the model to realistically capture observable deviations from the mean profile and to account for the natural heterogeneity in the population, and hence, the covariance structure. Based on the individual-specific fitted PSA curves, we estimated the change in PSA concentration for men from randomization up to PrCa diagnosis or 12 years of follow-up, whichever came first. By generating the PSA histories, we could estimate the time when a man with a PrCa would enter the

detectable preclinical phase of the disease, i.e. the cancer become potentially detectable by screening and when the hypothetical screening protocol would have been able to detect the elevated PSA, resulting in detection of the cancer by screening (diagnosis and subsequent commencement of treatment).

The simulation model for PrCa mortality was built sequentially. First, we estimated the probability of PrCa death during the first two years after randomization. Second, among those who survived the first two years, we estimated the probability of PrCa death between two and four years. Following this sequential construction, a set of probabilities was estimated from the data up to the last interval from 10 to 12 years. As multiple time intervals were obtained on the same individuals, these probabilities were estimated by using generalized estimating equations models with a complementary log-log link function including baseline age, centre, time interval, estimated log of PSA at the beginning of the time interval, and finally, information on whether the individual was screen-positive at the beginning of the time interval, as covariates. Men with no PSA measurements (non-participants and control arm) were not included in the estimation of the model parameters.

Once the set of probabilities was established, we simulated hypothetical data by bootstrap resampling from this model under the following scenarios:

- The Swedish screening protocol with two-year screening interval addressing whether PrCa mortality in the screening arms of the Netherlands and Finland would have been improved relative to the control arm. In this scenario, the Finnish individuals would have become screen positive earlier as the delay to reach the threshold of 3 ng/ml would have been shorter due to more frequent screening and lower threshold, and the Dutch men due shorter screening interval.
- No screening-scenario expected to result in similar PrCa mortality in the intervention and the control arms. This means that men would have never become screen positive, regardless of the longitudinal development of PSA. The scenario was intended to show whether the effects of screening have been correctly estimated by the simulation model.
- Simulation with similar procedures as actually applied in each centre. This was used as a second validation of the simulation model expected to yield results similar to those actually observed.

Men in the control arm in each centre were used as observed, without simulation.

The times of death overall were assumed to be uniformly distributed on the time interval when PrCa death occurred.

The simulation model is particularly designed for ERSPC and addressing the current research question and is similar to the FHCRC model in the implementation of PSA model part (<https://resources.cisnet.cancer.gov/registry/packages/psapc-fhcrc/>). Full details are given in the Appendix.

3. Results

The PSA model indicated statistically significant differences between the centres, with the highest levels in Finland, followed by Sweden and the Netherlands in that order (Table A.2). The linear component for age in the model indicated a steady increase in the average PSA levels with a quadratic age component depicting a small, but statistically significant deceleration in the velocity. Men with Gleason score >7 tumors showed the largest acceleration in the PSA development five years prior to the actual diagnosis, but substantial changes were also observed in men with Gleason score 7 or <7 cancers. The random effects part of the model (not shown)

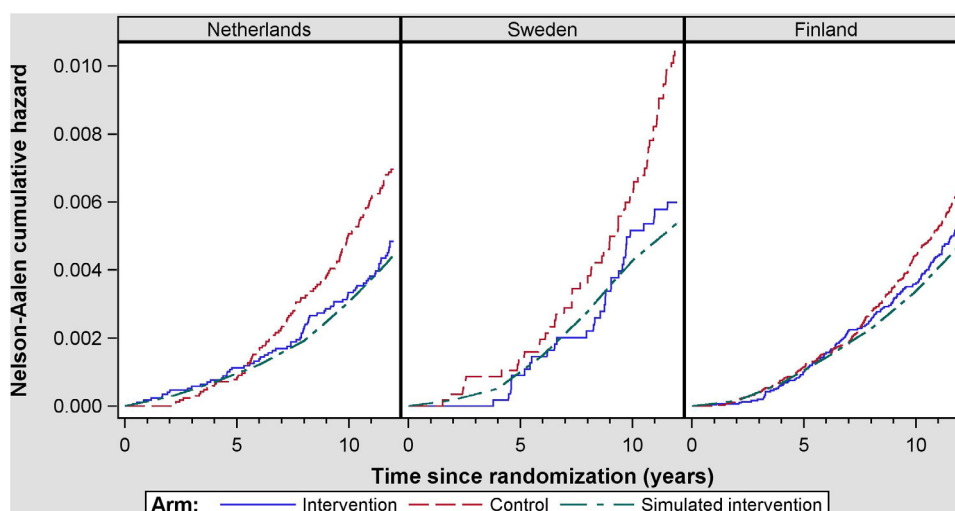


Fig. 1. Cumulative hazard of prostate cancer in the intervention arm, control arm and simulated arms under the Swedish screening protocol.

showed marked variation between individual men and underlined the importance of predicting the PSA at different times with a delicate balance between observed individual data and the average PSA development for similar men (Figure A.1).

Fig. 1 shows the Nelson-Aalen estimates of the cumulative hazard of PrCa death for the hypothetical intervention arm, if the Swedish protocol would have been applied in all of the centres, as well as the observed cumulative hazard for the actual intervention and control arms. Unsurprisingly, there would have been no change in PrCa mortality in Sweden, because the hypothetical intervention arm was constructed under the screening protocol used in Sweden. The hypothetical intervention arms for the Netherlands and Finland indicate that screening every two years with a lower PSA threshold than was used in Finland would have affected PrCa mortality only slightly, as the estimated cumulative hazards of the hypothetical intervention arms improved very little compared to the actual results based on the observed data in the intervention arms. Moreover, the observed cumulative hazards, for instance at 10 years, were 0.00334 in the Netherlands and 0.00359 in Finland, i.e. close to the midpoints of the 95% confidence intervals (CI) of the cumulative hazards of the hypothetical (simulated) intervention arms. The symmetric CI (0.00230–0.00391 in the Netherlands and 0.00276–0.00402 in Finland) also indicates consistency of the actual screening outcomes and those obtained using a hypothetical alternative screening algorithm, pointing to only a small contribution of the simulated screening features.

Table 1 shows the results in terms of observed and simulated PrCa mortality in the intervention arm. The median number of PrCa deaths in Finland across simulations was 151, slightly higher than

the observed 148 PrCa deaths, with comparable PrCa mortality rates (0.43 and 0.40 per 1000 person-years). Similarly, the observed and simulated PrCa mortality rates in the Netherlands were closely similar, 0.38 and 0.37. Also the ratio of observed and simulated mortality were close to one, the confidence intervals covering unity (with a wide margin on both sides) and perfectly in line with Fig. 1, providing supportive evidence that the difference between the screening protocols (as captured by the simulation) explains only a small part of the difference between the centres.

Fig. 2 (top row) shows that the simulation model reconstructed the observed data of the intervention arm with high agreement with the ERSPC screening protocols. The graphs in the bottom row of Fig. 2 shows that the model, and the screening effects within it, represent well the risk in the absence of screening, because the hypothetical “intervention” arms without screening closely matched the observed control arms both in Sweden and the Netherlands. During the first five to six years of follow-up, the PrCa mortality in the actual control arm in the Netherlands was lower than observed in the intervention arm and obtained by the simulation model for the hypothetical non-screened intervention arm. However, the PrCa mortality in the control arm caught up with the simulated intervention arm without screening, and behaved thereafter as predicted by the simulation model. Finland showed a completely different pattern: observed PrCa mortality in the control arm was consistently lower than predicted by the simulation of the hypothetical intervention arm in the absence of screening.

In a model-based simulation, assuming that 20% of the men in the control arm would have received similar screening as in the intervention arm (“effective contamination”) and 80% of the men

Table 1

Observed and simulation-based prediction of PrCa mortality by centre due to the implementation of the Swedish screening protocol within each centre.

Observed data				Model simulated data (1000 simulated data sets)			Simulated vs observed
Centre	Number of PrCa deaths	Person years	Rate per 1000 person years	Median number of PrCa deaths (IQR) ^a	Median number of person years (IQR) ^a	Rate per 1000 person years (95% CI)	Rate ratio (95% CI)
Finland	148	346,038	0.43	151 (142–160)	381,845 (381,796–381,887)	0.40 (0.34–0.46)	0.92 (0.78–1.07)
The Netherlands	73	189,685	0.38	76 (71–82)	207,588 (207,552–207,623)	0.37 (0.29–0.45)	0.96 (0.76–1.17)
Sweden	31	64,489	0.48	32 (27–35)	70,673 (70,652–70,692)	0.45 (0.31–0.62)	0.93 (0.65–1.30)

^a Medians and interquartile ranges (IQR) were computed across the simulated data sets within each centre.

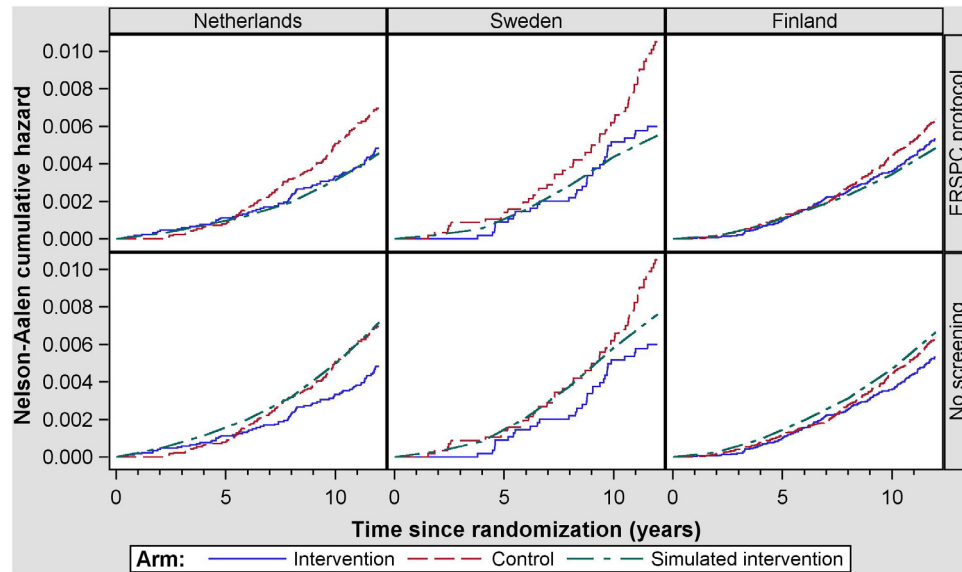


Fig. 2. Model validation results. Top row of plots shows that the simulation model is able to produce consistent data to what was actually observed (the simulated intervention arm vs. the intervention arm) under the ERSPC screening protocols. The bottom row shows the expected results in absence of screening.

remained unscreened, resulted in similar PrCa mortality to what was observed at 12 years (Fig. 3).

4. Discussion

The study hypothesis that the differences between ERSPC study centres were due to differences in screening protocols was not supported by the findings of the present simulation study. Only marginal additional PrCa mortality reduction could have been obtained in Finland and in the Netherlands by implementing the Swedish screening protocol. The finding is in line with two recent modelling studies [5,6], which found small differences in PrCa mortality between alternative screening strategies. Wu et al. [7] suggested that the PrCa mortality reduction could be more substantial with shorter interscreening intervals.

Based on the simulation, the PrCa mortality in the Finnish control arm is lower than expected in the absence of any screening.

The observation was detected only in Finland, but not in Sweden or the Netherlands. Together with a slightly less effective screening protocol, this accounts for the smaller relative screening effect in Finland. The most likely explanation for the lower-than-expected PrCa mortality in the Finnish control arm is contamination, i.e. opportunistic PSA testing among men in the control arm.

The evidence for opportunistic screening in the Finnish control arm is sparse. Ten percent of men in the screening arm have previously reported having a PSA test before the first screening round of the trial [8]. In a survey of attitudes among Finnish physicians, the frequency of reported regular PSA testing among asymptomatic men declined from 18% to 9% between 1999 and 2007 [9]. More recently, it has been estimated that 50% of the men in the control arm in Finland have been tested at least once in the first eight years of follow-up (unpublished data). Such a high contamination rate in the control arm is bound to reduce the difference in PrCa mortality between the screening and control

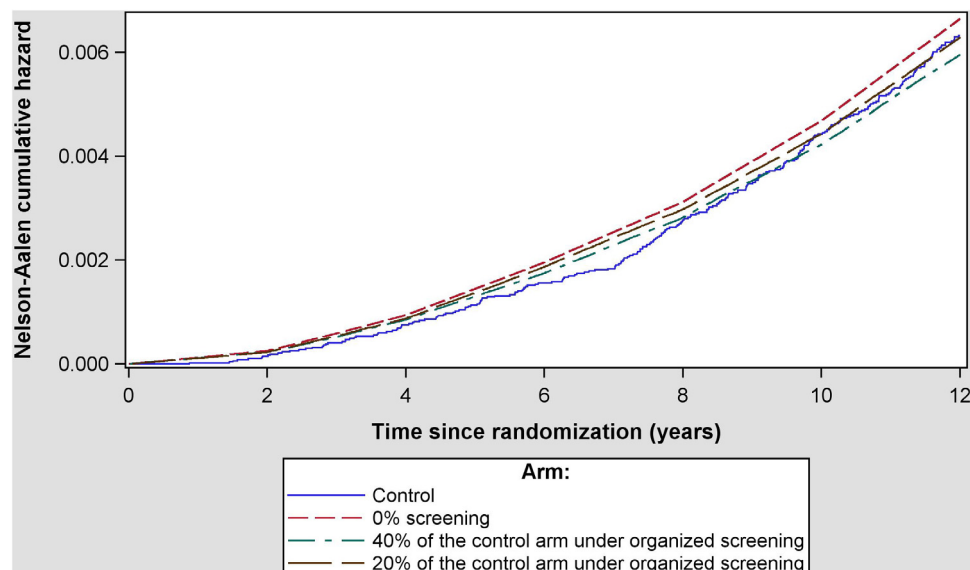


Fig. 3. Model-based simulation assessing the impact of adding organized screening to the hypothetical control arm without any screening ("0% screening").

arms in Finland. According to NORDCAN, a register-based cancer database for the Nordic countries (<http://www.dep.iarc.fr/NORDCAN/English/frame.as>), PrCa mortality in Finland in 2012 was 22.1 and in Sweden 29.9 in Sweden per 100,000 man-years. The clearly lower PrCa mortality in Finland supports this interpretation. During the conduct of ERSPC, PrCa mortality in Finland has declined from 18.7 in 1992–96 to 12.6 in 2012 (Finnish Cancer Registry, Cancer Statistics at www.cancerregistry.fi). NORDCAN figures are age-adjusted to European standard population and Finnish Cancer Registry figures are age-adjusted to world standard population. In the United States, Etzioni et al. [10] have suggested that, in addition to PSA screening, improvements in treatment have contributed to the decline in PrCa mortality.

Based on case-control studies, the evidence of the effect of unorganized screening by PSA and/or digital rectal examination on PrCa mortality is not consistent [11–15]. Ecological studies also show contradictory results [16–18].

In a recent comparison, the Swedish control arm of ERSPC showed no PrCa mortality improvement to pre-PSA era historical population data [19]. The extent of contamination in the Swedish control arm is unknown, however. It has also been estimated that noncompliance and contamination dilute the screening effect from a relative risk of PrCa mortality from 0.49 to 0.68 in the Dutch centre of the ERSPC [20].

Thus, effectiveness of opportunistic screening remains open, and is very likely to be inferior to an organised screening programme. Hence, a PrCa mortality reduction equivalent to 20% of the men being included in a screening programme in the control arm offers an underestimate of the extent of contamination. In reality, a larger proportion of men were probably tested, with gradual introduction and less systematic referral to diagnostic examinations leading to a similar number of cases receiving early treatment, as if 20% were screened in accordance with a rigorous protocol. Nevertheless, the 20% is very close to the published estimate of contamination in the Finnish control arm at four years.

However, in the light of the controversial evidence on the effect of unorganized and opportunistic screening, other explanations for the smaller screening benefit in Finland, such as differences in number of screens, proportion of positive tests or procedures taken based on PSA tests, are also possible.

The simulation proved to be realistic and useful in assessing the differences between the study centres. A weakness of the model is that the PrCa diagnosis was only indirectly incorporated in the simulation model, by elevation of the PSA levels prior to the diagnosis. We could not reliably evaluate how more frequent screening would influence the number of cancers detected and the timing of the diagnosis without imposing restrictive and uncertain assumptions. Such assumptions could not have been verified and would have had a substantial effect on the results. They were therefore not introduced, but left as an indirect component. The simulation proved realistic and sensitive, and is potentially useful for estimation of effects of alternative screening protocols elsewhere as well.

These results indicate that opportunistic screening dilutes the screening effects on PrCa mortality in the Finnish centre. As Finland is the largest single centre in ERSPC, maximal efficiency of PrCa screening is most likely to be greater than has been reported in ERSPC, provided that there are no other factors which may influence outcomes in Finland. ERSPC is likely to be affected by contamination, though unlikely as strongly as PLCO [21].

New insights from the current study should be considered when revising the recommendations on PSA based PrCa screening. Choice between PSA cut-off (3 vs 4 ng/ml) and screening interval (2 vs 4 years) do not seem to be major determinants of screening effect, and therefore less intensive screening algorithm in these respects may be preferred to reduce costs and adverse effects (overdiagnosis). Prevalence of opportunistic screening, on the

other hand, should be considered when assessing the expected effect of prostate cancer screening.

Conflict of interest

The authors report no conflicts of interest.

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Author contributions

The authors listed below have made substantial contributions to the intellectual content of the paper in the various sections described below.

Auvinen, Nevalainen: Conception and design.

Tammela, Auvinen, Roobol, Schröder, Talala: Acquisition of data.

Nevalainen, Stenman, Roobol, Carlsson, Schröder, Auvinen: Analysis and interpretation of data.

Nevalainen, Stenman, Roobol, Carlsson, Schröder: Drafting of the manuscript.

Nevalainen, Stenman, Tammela, Roobol, Carlsson, Talala, Schröder: Critical revision of the manuscript for important intellectual content.

Nevalainen: Statistical analysis.

Auvinen: Supervision.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.canep.2016.11.005>.

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